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Exploring the relation between changes in NT-proBNP and renal function in patients with suspected heart failure using structural equation modelling

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Running Title: Changes in NT-proBNP and renal function in suspected heart failure

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Abstract

Background: The relation between changes in NT-proBNP and renal function has commonly been studied using multiple regressions, which may ignore the complexity of relations between related variables.

Methods and Results: Data were collected from patients referred with suspected heart failure (HF) to a community service. Structural equation modelling (SEM) was used to assess the association between changes in NT-proBNP at 1 year, and other pre-specified variables including age, sex, BMI, eGFR, loop diuretics and ACE inhibitor. Of 1006 patients with a follow-up NT-proBNP at 1 year, 882 (88%) had HF. The baseline median age was 72 (IQR: 63-78) years, 732 (73%) were men, 668 (66%) had left ventricular systolic dysfunction and 769 (76%) had NT-proBNP>400pg/ml. For all patients at 1 year, 243 (24%) patients had at least a 50% reduction in NT-proBNP, and 199 (20%) had at least a 50% increase, only 40 (3%) had <3% change. Change in NT-proBNP was strongly associated with baseline NT-proBNP (the standardized coefficient (r) = 0.73, $p<0.001$). The change in NT-proBNP was not associated with changes in eGFR, and was indirectly related with age, BMI, eGFR and loop diuretics ($p<0.01$ for all).

Conclusions: Baseline NT-proBNP was the main determinant of change in NT-proBNP at one year.

Introduction

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and renal dysfunction measured by urea or creatinine are strongly related to prognosis in patients with chronic heart failure (CHF). The higher the NT-proBNP and the worse the renal function, the worse the outcome. There are strong positive associations between adverse outcome and age, NT-proBNP, urea or creatinine.^{1, 2, 3, 4} There is a moderate, but significant, relationship between NT-proBNP and renal function.^{5, 6, 7} The better the renal function, the lower the NT-proBNP. Renal dysfunction affects NT-proBNP;^{8, 9, 10, 5} but a raised NT-proBNP concentration almost defines that heart failure is present, regardless of the severity of renal dysfunction.⁵ NT-proBNP is stronger predictor of outcome than renal function.^{11, 12} Studies further indicate that changes in NT-proBNP are significantly associated with mortality.^{13, 14} Patients with a fall in NT-proBNP have a better prognosis, and those with a rise have a worse prognosis.

The factors associated with change in NT-proBNP include age, sex and body mass index (BMI). There is a positive relationship between age and NT-proBNP.^{15 16} Women were more likely to have a high NT-proBNP,¹⁷ and there is an inverse relation between BMI and NT-proBNP.^{18 19}

In general, the inter-relationships between NT-proBNP, urea or creatinine, age and BMI have principally been studied by traditional multiple linear regression analysis, which explores a correlation between one dependent variable and the number of independent variables; this may ignore the complexity of relations between related variables. The purpose of the study was to use structure equation modes (SEM) path analysis²⁰ to assess the relations between changes in NT-proBNP at 1 year and pre-specified variables known to be associated with NT-proBNP: age, sex, BMI, eGFR, loop diuretics, ACE inhibitor (ACEi). Changes in BMI and changes in eGFR were also considered. Our hypothesis was that absolute changes in NT-proBNP during the first year's follow up are related to baseline value of NT-proBNP and renal function and also related to age, loop diuretics and changes in renal function (Figure 1).

Methods

Study population

Patients referred for the assessment of possible heart failure to a local heart failure clinic (Kingston-upon-Hull, UK) between the years 2002 and 2010 had symptoms, signs, electro- and echocardiograms recorded and blood samples taken for routine haematology and biochemistry including urea. The NT-proBNP samples were collected in ethylene-diamine-tetra-acetic tubes, spun at 3000 r.p.m for 15 minutes in a cooled (4°C) centrifuge and the plasma was stored at -80°C until batch analysed. The assay used was the Elecsys proBNP (Roche Diagnostics, Basel, Switzerland). eGFR was calculated using modification of diet in renal disease (MDRD) formula based on 4 variables: serum creatinine, age, ethnicity and gender. Patients had further routine clinic visits at one year.

Heart failure was defined as: symptoms compatible with a diagnosis of heart failure in the presence of: either left ventricular ejection fraction (LVEF) <40% (or equivalent) or NT-proBNP >400pg/ml. All patients provided written informed consent for their data to be used and the study was carried out in accordance with the Declarations of Helsinki and the European Standards for Good Clinical Practice. Ethical approval was granted by the Hull and East Yorkshire Local Research Ethics Committee.

Statistical analysis

The characteristics of patients are described by three different groups: a) all patients; b) heart failure; and c) patients in whom heart failure was excluded. Continuous variables are expressed as median and inter-quartile range and categorical variables as frequency and proportion. The continuous variables were tested for normality of distribution using Kolmogorov-Smirnov test. Structural equation modelling (SEM) was used to study associations between changes in NT-proBNP with pre-specified variables included baseline level NT-proBNP, eGFR, age, sex, BMI, loop diuretics, ACE inhibitor, changes in BMI and changes in eGFR. The change was measured as an absolute change between baseline and 1 year follow-up visit. Log transformation of NT-proBNP was used to meet the assumption of the model. Scatter plots and Pearson correlation coefficients were used initially to investigate correlations.

We used path analysis, a special case of structural equation modelling (SEM)^{20 21} in which a number of multiple regression models is considered simultaneously. SEM explores more complex relationships between variables than traditional regression analysis and includes

measurement error. SEM path modelling links direct and indirect variables through a medium variable, and thus an individual variable can be both an independent variable and a dependent variable at the same time. There are two stages to path analysis: an initial path model is constructed; and then the relative strength of each independent variable on the dependent variable is estimated. We estimated the model parameters using maximum likelihood estimation; chi-square, Comparative Fit Index (CFI)²² and Root Mean Square Error of Approximation (RMSEA)²³ were used to evaluate the goodness of model fit. Chi-square>0.05, RMSEA<0.05 and CFI>0.9 indicate that the model fits the data well. Assumptions of linearity were tested in each linear regression. Statistical analysis was carried out using SPSS 19 software. The level of statistical significance was set at $p=0.05$ with two tails.

Results

Patient characteristics are shown in Table 1. Of 1006 patients with a follow-up NT-proBNP at 1 year, the median age was 72 (IQR: 63-78) years, 732 (73%) were men, 662 (66%) had LVSD and 769 (76%) had NT-proBNP>400pg/ml at baseline. Age, urea, creatinine, left atrial dimension and heart rate were higher, and eGFR, QRS width, systolic BP and BMI were lower, in patients with HF compared with those without HF. For all patients at one year, 243 (24%) patients had at least a 50% reduction in NT-proBNP, 199 (20%) had at least a 50% increase. Only 40 (3%) had <3% change (Figure 2).

Table 2 shows the changes in variables at one year for the whole population and for patients with HF. The median NT-proBNP fell but renal function worsened at one year follow up compared with baseline for both populations ($p<0.001$ for all). There was a strong linear correlation between baseline BMI and changes in BMI at 1 year ($r=0.86$, $p<0.001$). The scatter plots in Figure 3-4 showed the relations between baseline and 1 year for NT-proBNP and eGFR, respectively.

The SEM model fitted the data well (chi-square = 18.55, $df = 10$, $p=0.05$, CFI = 0.995, RMSEA = 0.029) implies that there is no reason to reject the relationships hypothesized in the original model. Table 3 shows the results. Change in NT-proBNP was most strongly related to baseline NT-proBNP (the standardized coefficient (r) was 0.73, $p<0.001$). Lower eGFR at baseline was slightly associated with an increase in NT-proBNP ($p=0.06$), and there

was a weak negative correlation between change in eGFR and change in NT-proBNP ($p=0.07$). Change in NT-proBNP was not related to age and loop diuretics. The model accounted for 56% of the variance in change NT-proBNP at 1 year. Baseline NT-proBNP was strongly, positively related to age and taking loop diuretics ($p<0.01$ for all), and was negatively related to eGFR and BMI ($p<0.01$). Change in BMI were negatively related to baseline BMI and age ($r=-0.30$ for baseline BMI, $r=-0.14$ for age, $p<0.01$ for both), this means that the higher the BMI at baseline, the greater decrease in BMI at 1 year. Change in BMI was also slightly related with taking loop diuretics ($r=0.07$, $p=0.01$). Changes in eGFR were negatively correlated to age, baseline eGFR and baseline NT-proBNP ($p<0.01$ for all). In addition, there was a strong negative correlation between age and eGFR ($r=-0.46$; $p<0.001$), and a negative correlation between age and BMI ($r=-0.23$, $p<0.01$).

There were the potential relationships between baseline age, eGFR, loop diuretics and BMI with changes in NT-proBNP due to the strong correlation between changes in NT-proBNP and baseline NT-proBNP. Creatinine and urea were not included as they are highly correlated with eGFR. The similar results were found in patients with HF (not shown). The final relations between changes in NT-proBNP at 1 year with the other variables were shown in Figure 5.

Discussion

The structural equation modelling method used in this study demonstrated that change in NT-proBNP was mostly associated with baseline NT-proBNP. Changes in NT-proBNP were not directly correlated with age, BMI, eGFR and loop diuretics, but they are highly correlated with the baseline NT-proBNP, implying that a change in NT-proBNP was potentially related to age, BMI, eGFR and loop diuretics. The study showed that a change in NT-proBNP were not potentially associated with gender and ACE inhibitor.

Several studies indicated that renal dysfunction influences NT-proBNP.^{8 9 24 10 25} Our results confirmed the previous studies that there was a negative association between eGFR and NT-proBNP. One study²⁶ showed that the absolute change in NT-proBNP at 5 years was associated with poorer renal function (eGFR) (standardized coefficient (r) = -0.12, $p = 0.001$), this was similar with our study that changes in NT-proBNP at 1 year was negatively

associated with eGFR ($r = -0.03$, $p = 0.06$). Less information is available concerning the relationships between the changes in NT-proBNP and renal function.

The SEM path analysis studies the possible direct and indirect factors of the variable simultaneously. This method has been applied for cardiovascular research field although with very limited applications.^{27 28} Our study showed that change in NT-proBNP at 1 year was not only considered with baseline NT-proBNP but also included the factors that were associated through baseline NT-proBNP, such as age, BMI, eGFR and taking loop diuretic to exploring their potential relationships fully (total effects). The correlations obtained from SEM method are more robust compared with separate multiple regressions due to use correlated error terms. In contrast, traditional multiple regression models assume that all predictors are independent; however, in reality these independent variables are always correlated to each other in some degrees, such as eGFR and age. As far as we know, this is a first article to apply SEM method in the field to investigate the relation between changes in NT-proBNP and renal function. Hope this study will give insight into understanding the relationship between NT-proBNP and renal function further in patients with suspected HF.

Limitations

This study was an observational study; the time point at 1 year was not exactly same for all patients. We also found that baseline sinus rhythm was negatively associated with baseline NT-proBNP (SR vs not SR, $p < 0.001$) and changes in NT-proBNP (SR vs not SR, $p < 0.001$) but their correlations were not very strong and were not included into the study.

Conclusions

In a model including age, sex, BMI, eGFR, loop diuretics, ACE inhibitor and NT-proBNP measured at baseline and follow-up, baseline NT-proBNP was the main determinant of subsequent change in NT-proBNP at 1 year.

Acknowledgments:

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Figure legend

Figure 1: The path diagram showing the relationships amongst the variables: age, sex, BMI, eGFR, loop diuretics, ACE inhibitor, log10(NT-proBNP), changes in BMI, changes in eGFR and changes in log(NT-proBNP) from baseline to 12 months for the whole population. A line with one arrow represents a relationship between two variables, and the variable with the arrow pointing toward it is the dependent variable such as LogBNP_BL and LogDiff_BNP, and the other is the independent variable. The line with two arrows represents a possible correlation between the two variables. The e1, e2, e3 and e4 in circle represent error terms.

Below are abbreviations for variables used in Figure 1:

Age_BL: age at baseline

BMI_BL: BMI at baseline

eGFR_BL: eGFR at baseline

ACE_BL: ACE inhibitor at baseline

Loop_BL: loop diuretics at baseline

LogBNP_BL: log(NT-proBNP) at baseline

AbsoluteChangeBMI: an absolute change in BMI from baseline to 1-year

AbsoluteChangeGFR: an absolute change in eGFR from baseline to 1-year

LogDiff_BNP: an absolute change in NT-proBNP from baseline to 1-year, and then with a log-transformation.

Figure 2: % changes of NT-proBNP

Figure 3: Scatter plot between log(NT-proBNP) at 1 year and baseline ($r=0.76$, $p<0.001$)

Figure 4: Scatter plot between eGFR at 1 year and baseline ($r=0.81$, $p<0.001$)

Figure 5: The significant relationships ($p<0.05$) between changes in NT-proBNP (LogDiff_BNP) and variables: age, sex, BMI, eGFR, ACEi, loop diuretics, log(NT-proBNP), changes in BMI and changes in eGFR from baseline to 12 months apart from the relationships between changes in NT-proBNP with changes in eGFR ($p=0.07$) and baseline eGFR($p=0.06$), and the relationship between taking loop diuretics and changes in eGFR ($p=0.05$) using structure equation modelling for the whole cohort of patients ($n = 1006$). The number (a standardized regression coefficient) shows how each independent variable influences the dependent variable. The higher the value the greater the impact of the independent variable on the dependent variable. The detailed information was shown in Table 3.

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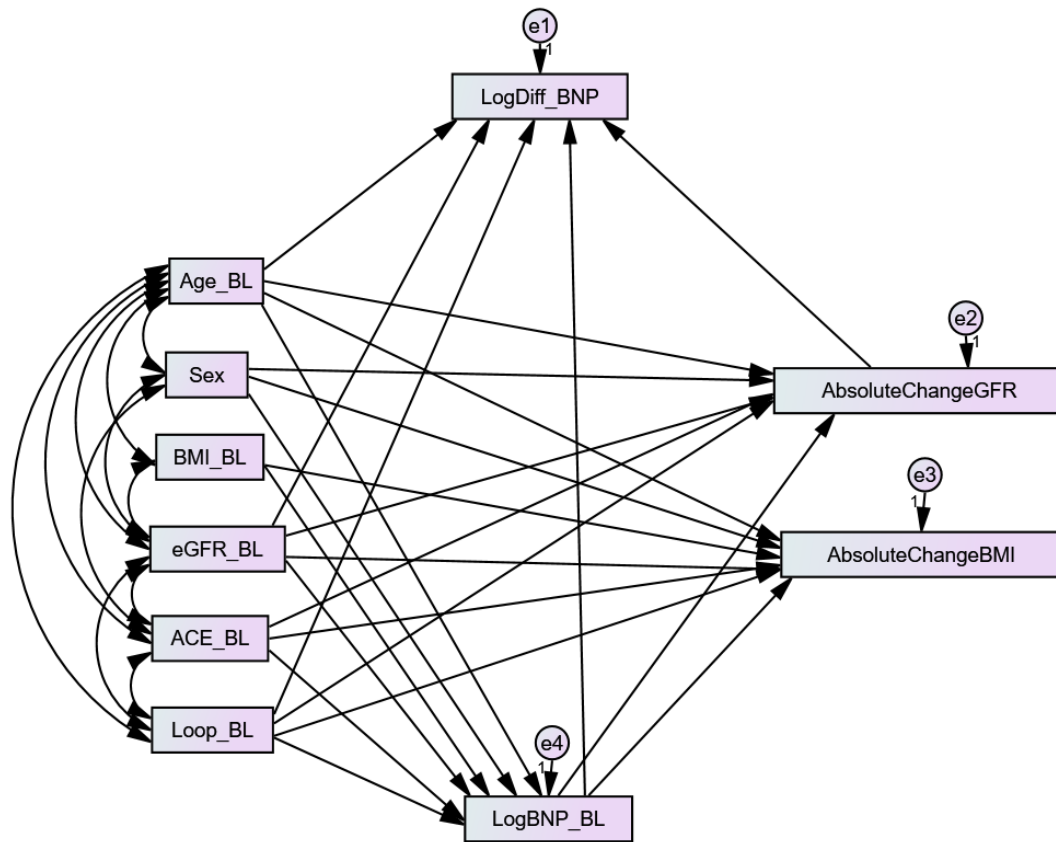


Figure 1: The path diagram showing the relationships amongst the variables: age, sex, BMI, eGFR, loop diuretics, ACE inhibitor, log₁₀(NT-proBNP), changes in BMI, changes in eGFR and changes in log(NT-proBNP) from baseline to 12 months for the whole population. A line with one arrow represents a relationship between two variables, and the variable with the arrow pointing toward it is the dependent variable such as LogBNP_BL and LogDiff_BNP, and the other is the independent variable. The line with two arrows represents a possible correlation between the two variables. The e1, e2, e3 and e4 in circle represent error terms.

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eGFR_BL: eGFR at baseline;

ACE_BL: ACE inhibitor at baseline;

Loop_BL: loop diuretics at baseline;

LogBNP_BL: log(NT-proBNP) at baseline;

AbsoluteChangeBMI: an absolute change in BMI from baseline to 1-year;

AbsoluteChangeGFR: an absolute change in eGFR from baseline to 1-year;

LogDiff_BNP: an absolute change in NT-proBNP from baseline to 1-year, and then with a log-transformation.

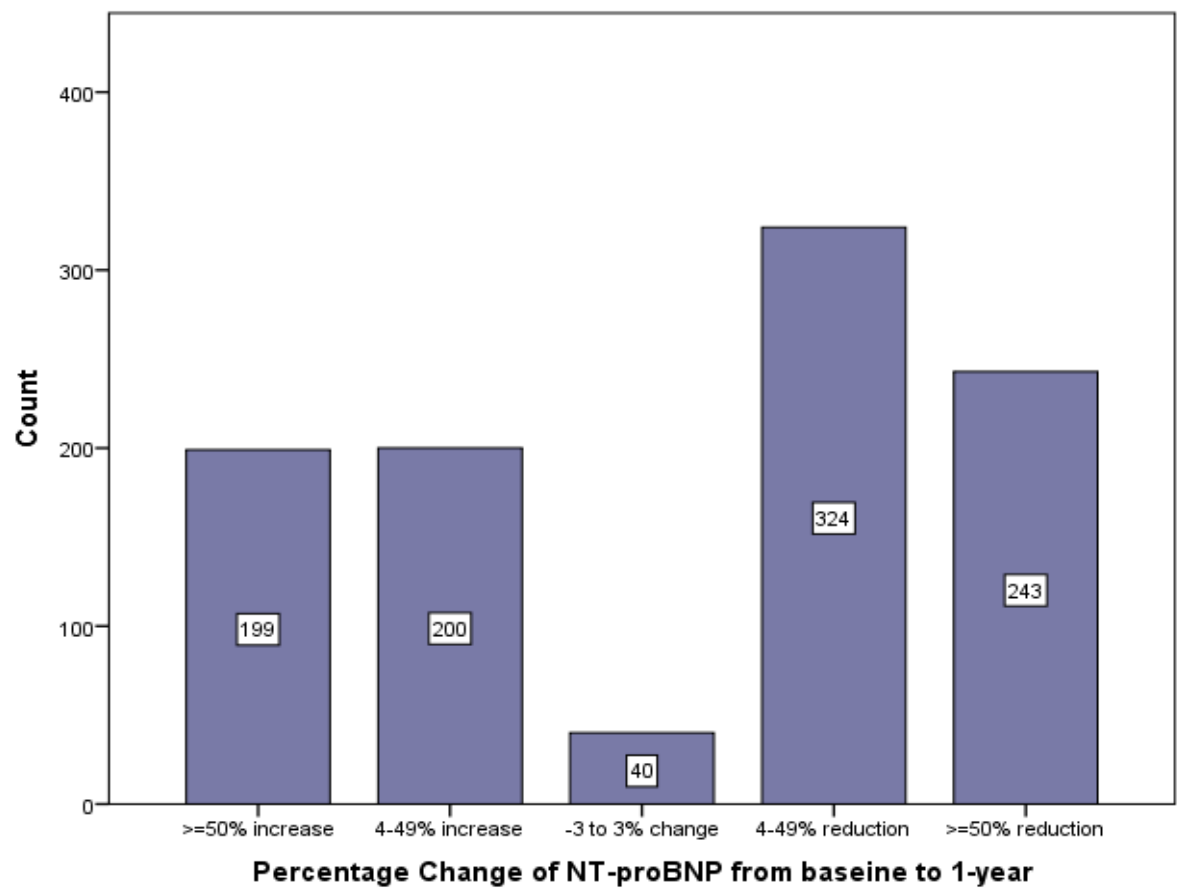


Figure 2: % changes of NT-proBNP

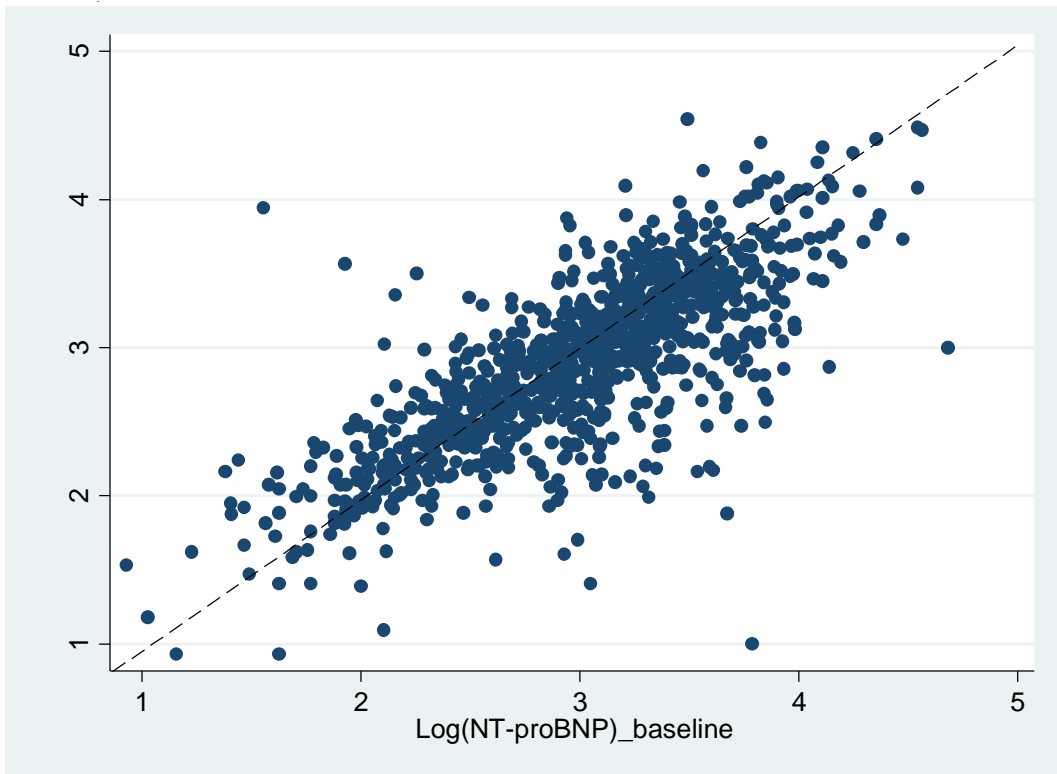


Figure 3: Scatter plot between log(NT-proBNP) at 1 year and baseline ($r=0.76$, $p<0.001$)

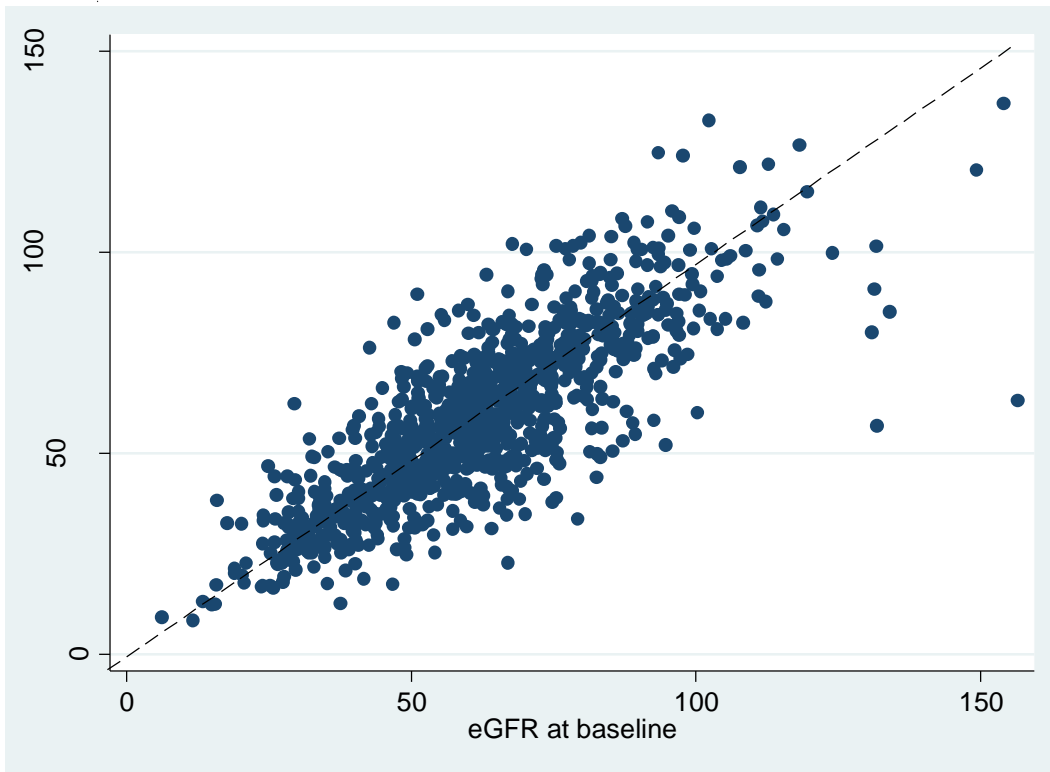


Figure 4: Scatter plot between eGFR at 1 year and baseline ($r=0.81$, $p<0.001$)

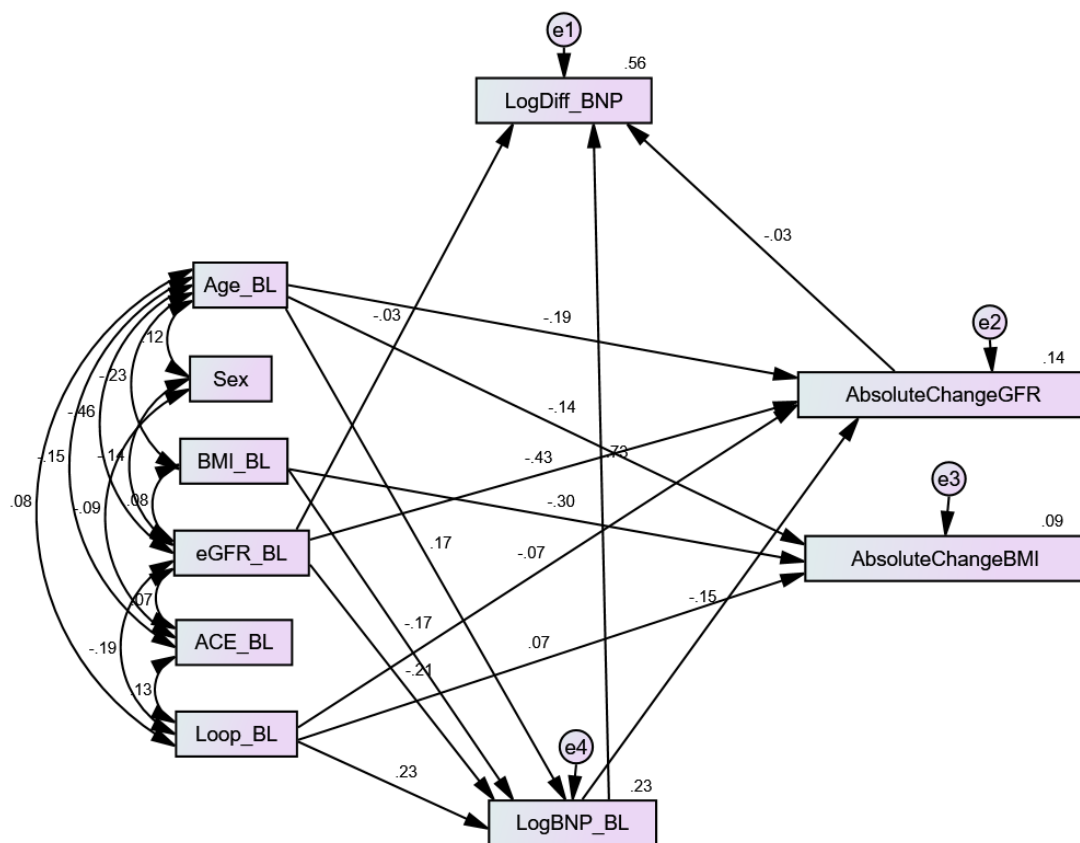


Figure 5: The significant relationships ($p < 0.05$) between changes in NT-proBNP (LogDiff_BNP) and variables: age, sex, BMI, eGFR, ACEi, loop diuretics, log(NT-proBNP), changes in BMI and changes in eGFR from baseline to 12 months apart from the relationships between changes in NT-proBNP with changes in eGFR ($p = 0.07$) and baseline eGFR ($p = 0.06$), and the relationship between taking loop diuretics and changes in eGFR ($p = 0.05$) using structure equation modelling for the whole cohort of patients ($n = 1006$). The number (a standardized regression coefficient) shows how each independent variable influences the dependent variable. The higher the value the greater the impact of the independent variable on the dependent variable. The detailed information was shown in Table 3.

Table 1: Baseline characteristics by three groups of the patients: whole population, patients with HF and patients in whom HF was refuted (not HF)

	Missing values (N)	Whole population (n=1006)	HF (n = 882)	Not HF (n =124)
Age (years)	0	72 (63-78)	72 (64-78)	70 (61-75)
Sex (male)	0	732 (73%)	651 (74%)	81 (65%)
IHD (yes)	0	625 (62%)	554 (63%)	71 (57%)
Diabetes	0	213 (21%)	187 (21%)	26 (21%)
BMI	0	27.9 (24.9-31.4)	27.8 (24.8-31.2)	29.5 (25.8-34.0)
COPD (yes)	0	106 (11%)	89 (10%)	17 (14%)
Sinus rhythm (yes)	0	630 (63%)	529 (60%)	101 (82%)
QRS width (msec)	96	108 (96-138)	111 (96-140)	97 (88-108)
NYHA class (III/IV)	0	295 (29%)	276 (31%)	19 (15%)
Systolic BP	53	132 (117-148)	131 (116-147)	139 (120-159)
Heart rate	82	69 (60-82)	70 (60-83)	64 (57-76)
LVI > Mild	0	668 (66%)	668 (76%)	0
Left atrial dimension (cm)	0	4.2 (3.8-4.8)	4.3 (3.9-4.8)	3.8 (3.5-4.3)
NT-proBNP (pg/ml)	0	1106 (423-2605)	1340 (652-2935)	162 (88-272)
NT-proBNP>400 pg/ml	0	769 (76%)	769 (87%)	0
Sodium (mmol/L)	0	139 (137-141)	139 (137-141)	140 (138-142)
Potassium (mmol/L)	3	4.4 (4.1-4.7)	4.4 (4.1-4.7)	4.4 (4.1-4.7)
Urea (mmol/L)	0	6.7 (5.2-9.0)	6.8 (5.3-9.2)	5.9 (4.5-7.6)
Creatinine (umol/L)	0	102 (86-125)	103 (87-128)	89 (80-105)
eGFR (ml/min/1.73m ²)	0	62 (49-75)	61 (48-74)	68 (60-83)
Hb (g/dL)	46	13.6 (12.5-14.7)	13.6 (12.3-14.7)	13.8 (12.9-14.7)
Loop diuretics (yes)	0	673 (67%)	621 (70%)	52 (42%)

IHD, ischaemic heart disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NYHA class, the New York Heart association; LVI, left ventricular impairment; eGFR, estimated glomerular filtration rate; Hb, haemoglobin.

Table 2: Patients characteristics at baseline and follow up at one year with median and IQR

	All patients			Heart Failure		
	Baseline	1 year	p-value*	Baseline	1 year	p-value*
BMI	27.9 (25.0-31.4)	28.0 (25.0-31.8)	0.038	27.8 (24.8-31.2)	27.9 (24.9-31.6)	0.042
NT-proBNP (pg/ml)	1106 (423-2608)	871 (330-2003)	<0.001	1340 (652-2935)	1040 (448-2226)	<0.001
Urea (mmol/L)	6.7 (5.2-9.0)	7.1 (5.4-10.1)	<0.001	6.8 (5.3-9.2)	7.3 (5.5-10.5)	<0.001
Creatinine (umol/L)	102 (86-125)	106 (88-135)	<0.001	103 (87-128)	108 (90-137)	<0.001
eGFR (ml/min/1.73m ²)	61.9 (49.4-75.1)	58.7 (44.3-73.9)	<0.001	61.2 (47.9-74.0)	56.9 (42.8-72.6)	<0.001

*Paired t-tests were used

Table 3: The variables influencing NT-proBNP, changes in BMI, changes in eGFR and changes in NT-proBNP from baseline to 1 year using SEM method

	Baseline NT-proBNP*				Changes in NT-proBNP *				Changes in BMI				Changes in eGFR			
	Estimate d coefficie nt	S.E.	Standardi zed coefficie nt	p-value	Estimat ed coeffici ent	S.E.	Standardi zed coefficie nt	p-value	Estimat ed coeffici ent	S.E.	Standardiz ed coefficient	p-value	Estimate d coefficie nt	S.E.	Standardi zed coefficie nt	p- value
Age	0.01	0.002	0.17	<0.01	-0.003	0.002	-0.02	0.14	-0.02	0.01	-0.14	0.003	-0.23	0.04	-0.19	<0.01
Sex (male)	-0.05	0.037	-0.04	0.176	-	-	-	-	-	-	-	-	-1.08	0.86	-0.04	0.21
BMI	-0.02	0.003	-0.17	<0.01	-	-	-	-	-0.12	0.01	-0.30	<0.01	-	-	-	-
eGFR	-0.01	0.001	-0.21	<0.01	-0.002	0.001	-0.03	0.06	0.003	0.004	0.03	0.43	-0.27	0.02	-0.43	<0.01
Loop	0.28	0.036	0.23	<0.01	-0.02	0.04	-0.01	0.65	0.39	0.16	0.07	0.01	-1.65	0.85	-0.07	0.05
ACE	0.04	0.036	0.03	0.33	-	-	-	-	0.17	0.15	0.03	0.27	-1.14	0.83	-0.04	0.17
Log10(NT -proBNP)	-	-	-	-	0.97	0.03	0.73	<0.001	-0.21	0.13	-0.06	0.11	-3.29	0.71	-0.15	<0.01
Changes in BMI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Changes in eGFR	-	-	-	-	-0.002	0.001	-0.03	0.07	-	-	-	-	-	-	-	-
R ²	0.23				0.56				0.09				0.14			

* log transformation with base 10.

“ – “Assuming that there is no correlation between the two variables